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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,712	11/24/2003	Kenji Sugimoto	245901US0	9928
22850	7590	05/02/2007		
OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			EXAMINER DUNSTON, JENNIFER ANN	
			ART UNIT 1636	PAPER NUMBER
			NOTIFICATION DATE 05/02/2007	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/718,712	<b>Applicant(s)</b> SUGIMOTO ET AL.	
	<b>Examiner</b> Jennifer Dunston	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 07 February 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 21 and 43-47 is/are pending in the application.
- 4a) Of the above claim(s) 43,44,46 and 47 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21 and 45 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 June 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

This action is in response to the amendment, filed 2/7/2007, in which claims 1-20 and 22-42 were canceled, claims 21, 43 and 44 were amended, and claims 45-47 were newly added. Currently, claims 21 and 43-47 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Election/Restrictions*

Applicants elected Group I, and histone H3 (chromosome) and importin  $\alpha$  (nuclear membrane) species with traverse in the reply filed on 1/28/2005. Claims 21 and 45-46 read on the elected invention and elected species.

Claims 43, 44, 46 and 47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable product claim. New claims 46 and 47 read on Groups III and II, respectively, as set forth in the restriction requirement mailed 12/28/2004. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/28/2005.

Currently, claims 21 and 45 are under consideration.

***Claim Rejections - 35 USC § 103***

Claims 21 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugimoto et al (Molecular Biology of the Cell, Vol. 13, pages 50a-51a, Abstract 282, November 1, 2002, cited in a prior action; see the entire abstract) in view of Rusan et al (Molecular Biology of the Cell, Vol. 12, pages 971-980, April 2001; see the entire reference). This rejection was made in the Office action mailed 10/6/2006 and has been altered to address the amendments to the claims in the reply filed 2/7/2007.

Sugimoto et al teach a human stable cell line comprising polynucleotides encoding three fusion proteins: histone H3 fused to cyan fluorescent protein (CFP-histone H3), importin  $\alpha$  fused to red fluorescent protein (DsRed-importin $\alpha$ ), and Aurora-A fused to green fluorescent protein (GFP-Aurora-A) (paragraph bridging pages 50a-51a). CFP-histone H3, DsRed-importin $\alpha$ , and EGFP-Aurora-A localize to the following cell structures: chromosome, nuclear membrane, and centrosome, respectively, and can be used to monitor cell division (paragraph bridging pages 50a-51a).

Sugimoto et al do not teach the cell comprising a polynucleotide encoding a fusion protein comprising  $\alpha$ -tubulin-GFP.

Rusan et al teach LLC PK-1 $\alpha$  cells comprising a commercially available polynucleotide encoding a fusion protein comprising  $\alpha$ -tubulin and green fluorescent protein (GFP) (e.g. page 973, Transfection and paragraph bridging columns). Microtubules containing the GFP-  $\alpha$ -tubulin localize to and are released from the centrosome (e.g. Figure 4), and thus  $\alpha$ -tubulin is a centrosome polypeptide. Rusan et al teach that the cells expressing GFP-  $\alpha$ -tubulin are suitable for monitoring microtubule dynamic instability during mitosis (e.g. page 975). Rusan et al teach

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that it within the skill of the art to make numerous different GFP-tubulin fusion constructs (e.g. paragraph bridging pages 971-972). Furthermore, Rusan et al teach that prior to the development of a polynucleotide encoding GFP- $\alpha$ -tubulin, it had been extremely difficult to directly measure microtubule dynamics in mammalian cells throughout the cell cycle and that the availability of cells expressing GFP-  $\alpha$ -tubulin should provide a simple, easily manipulated system to examine microtubule behavior in mammalian cells (e.g. page 972, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the cell comprising polynucleotides encoding three different fusion proteins of Sugimoto et al to replace the polynucleotide encoding Aurora-A-GFP with the polynucleotide encoding GFP- $\alpha$ -tubulin of Rusan et al because Sugimoto et al and Rusan et al teach it is within the ordinary skill in the art to make and use a polynucleotide encoding a cell structure protein fused to a green fluorescent protein.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to examine microtubule behavior in living mammalian cells in a simple and easily manipulated system as taught by Rusan et al and being able to visualize the chromosomes and nuclear membrane at the same time as taught by Sugimoto et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

***Response to Amendment – Declaration of Dr. Sugimoto***

The declaration under 37 CFR 1.132 filed 2/7/2007 is insufficient to overcome the rejection of claims 21 and 45 based upon the Sugimoto and Rusan references as set forth in the last Office action.

The declaration provides evidence of clearer visualization of microtubule organization centers and aster, as well as microtubules, with the  $\alpha$ -tubulin-GFP protein as compared to the Aurora A-GFP protein. However, this result is not unexpected in light of the teachings of the Rusan reference. The figures of the Rusan reference demonstrate clear visualization of the MTOC, aster and microtubules in dividing cells. Further, Rusan et al recognized that the use of  $\alpha$ -tubulin-GFP would overcome the difficulties in the art with observing microtubules during cell division and note that the availability of cells expressing  $\alpha$ -tubulin-GFP should provide a simple, easily manipulated system to examine microtubule behavior in mammalian cells (pages 11-12 of the Office action mailed 10/6/2006). Moreover, at the time the invention was made, one would appreciate the differences in expression obtained with labeled tubulin as compared to labeled Aurora A. Comparison of the expression pattern of the  $\alpha$ -tubulin-GFP of Rusan et al to the Aurora-A-EGFP expression of the prior art (Meraldi et al. EMBO Journal, Vol. 21, No. 4, pages 483-492, February 2002; e.g. Figures 1A, 2A, 3A and 4A) demonstrates a clearer visualization of the mitotic spindle and microtubules throughout cell division with  $\alpha$ -tubulin-GFP as compared to Aurora-A-EGFP. Thus, the results obtained in the comparison of  $\alpha$ -tubulin-GFP to Aurora-A-GFP would not be unexpected to one of skill in the art at the time the invention was made.

Upon consideration of the evidence as a whole, the declaration of Dr. Sugimoto is insufficient to overcome the rejection of claims 21 and 45 under 35 U.S.C. 103(a) as being unpatentable over Sugimoto et al in view of Rusan et al.

***Response to Arguments - 35 USC § 103***

The rejection of claims 21-23, 25, 27, 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Gerlich et al in view of Rusan et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 2/7/2007.

The rejection of claims 21-25, 27, 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Gerlich et al in view of Rusan et al further in view of Kimura et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 2/7/2007.

The rejection of claims 21-23, 25, 27, 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Gerlich et al in view of Rusan et al further in view of Kim et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 2/7/2007.

With respect to the rejection of claims 21 and 45 under 35 U.S.C. 103(a) as being unpatentable over Sugimoto et al in view of Rusan et al, Applicant's arguments filed 2/7/2007 have been fully considered but they are not persuasive.

The response asserts that neither Sugimoto or Rusan disclose a cell expressing the three types of fusion proteins required by the claims:  $\alpha$ -tubulin GFP, histone H3-CFP and Importin  $\alpha$ -DsRed. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

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combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The response asserts that Sugimoto does not suggest substituting  $\alpha$ -tubulin-GFP for Aurora-A-GFP. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Rusan et al teach that prior to the development of a polynucleotide encoding GFP- $\alpha$ -tubulin, it had been extremely difficult to directly measure microtubule dynamics in mammalian cells throughout the cell cycle and that the availability of cells expressing GFP-  $\alpha$ -tubulin should provide a simple, easily manipulated system to examine microtubule behavior in mammalian cells (e.g. page 972, left column). As stated on page 12 of the Office action mailed 10/6/2006, "One would have been motivated to make such a modification in order to receive the expected benefit of being able to examine microtubule behavior in living mammalian cells in a simple and easily manipulated system as taught by Rusan et al and being able to visualize the chromosomes and nuclear membrane at the same time as taught by Sugimoto et al."

The response asserts that the references do not provide a reasonable expectation of success that such a substitution would provide superior ability to visualize cell dynamics. This is not persuasive, because Rusan et al teach that prior to the development of a polynucleotide encoding GFP- $\alpha$ -tubulin, it had been extremely difficult to directly measure microtubule



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dynamics in mammalian cells throughout the cell cycle and that the availability of cells expressing GFP-  $\alpha$ -tubulin should provide a simple, easily manipulated system to examine microtubule behavior in mammalian cells (e.g. page 972, left column). Further, Rusan et al teach that GFP-  $\alpha$ -tubulin expressing cells will be a useful tool to elucidate the regulation of dynamic turnover throughout the cell cycle (e.g. page 979, Summary). Thus, Rusan teaches that the use of the GFP-  $\alpha$ -tubulin is an improvement over the prior art methods of visualization of microtubules.

The response asserts that the declaration of Dr. Sugimoto demonstrates that using GFP-  $\alpha$ -tubulin in place of Aurora-A-GFP results in improved visualization of the mitotic spindle through the process of cell division, clearer visualization of microtubule organization centers, and clearer visualization of mitotic spindles in metaphase to telophase. Rusan et al state, "Cells expressing GFP-tubulin have the potential to be an invaluable tool for studying microtubule dynamics, organization, and behavior throughout the cell cycle." See page 972, right column, 1<sup>st</sup> full paragraph. The results of Rusan et al provide evidence of clear visualization of the mitotic spindle during the process of cell division (e.g., Figures 1B, 2A and 4). Comparison of the expression pattern of the  $\alpha$ -tubulin-GFP of Rusan et al to the Aurora-A-EGFP expression of the prior art (Meraldi et al. EMBO Journal, Vol. 21, No. 4, pages 483-492, February 2002; e.g. Figures 1A, 2A, 3A and 4A) demonstrates a clearer visualization of the mitotic spindle and microtubules throughout cell division with  $\alpha$ -tubulin-GFP as compared to Aurora-A-EGFP. Thus, the results obtained in the comparison of  $\alpha$ -tubulin-GFP to Aurora-A-GFP would not be unexpected to one of skill in the art at the time the invention was made.

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The response asserts that Rusan does not teach or suggest a combination of  $\alpha$ -tubulin-GFP with other fusion proteins. This is not found persuasive, because Sugimoto et al teach a combination of a GFP fusion protein with H3-CFP and importin  $\alpha$ -DsRed.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

### ***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

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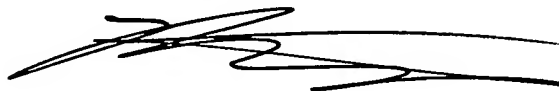
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.  
Examiner  
Art Unit 1636

jad

CELINE QIAN, PH.D.  
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to be 'C. Qian', written over a horizontal line.

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